EXPRESS MAIL CERTIFICATE

Date _____ Label No. _____
I hereby certify that, on the date indicated above, this paper or fee was deposited with the U.S. Postal Service & that it was addressed for delivery to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 by "Express Mail Post Office to Addressee" service.

Name (Print) _____ Signature _____

PLEASE CHARGE ANY DEFICIENCY UP TO $2,000.00 OR CREDIT ANY EXCESS IN THE FEES DUE WITH THIS DOCUMENT TO OUR DEPOSIT ACCOUNT NO. 04 – 0100

Customer No.: 07278 Docket No: 05432/100M029-US2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Serial No. : 10/750,049 Art Unit: Not Yet Assigned

Applicants : Hans PETERSEN et al.

Filed : December 30, 2003 Examiner: Not Yet Assigned

Title : CRYSTALLINE BASE OF CITALOPRAM

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION TO MAKE SPECIAL UNDER 37 C.F.R. §1.102

Sir:

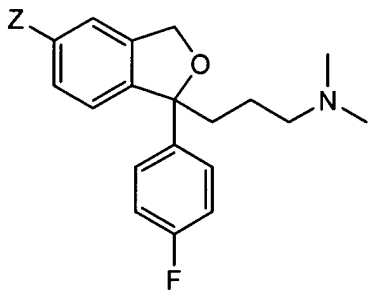
This is a petition pursuant to 37 C.F.R. §1.102(d) and M.P.E.P. §708.02(VIII) to advance the above-identified patent application out of turn for examination. This petition is accompanied by a check for $130.00 to cover the fee set forth in 37 C.F.R. §1.17(h).

03/19/2004 SZEWDIE1 00000032 10750049
01 FC:1460 130.00 OP

I. Claims Directed to a Single Invention

It is believed that the claims in the application are directed to a single invention. The present application includes one independent claim (claim 21). Claims 22-33 depend from claim 21.

Claims 21-33 are directed to a crystalline free base of citalopram that has a purity of at least 99.8% w/w and includes an impurity of the formula:



wherein Z is bromine or chlorine.

If the Examiner determines that all pending claims are not directed to a single invention, applicants will make an election without traverse as a prerequisite to the grant of special status.

II. Pre-Examination Search

A pre-examination search was made in International Class C 07D 307/87 by the Swedish Patent Office, as the International Searching Authority for the International counterpart (PCT Application No. PCT/DK01/00137) to this application during the International phase. The International Search Report (Exhibit 1), and the documents cited therein (Exhibits 2-4) are submitted herewith. Below

is a discussion of each of the references cited in the International Search Report, demonstrating how the claimed invention is patentable over them.

III. Discussion of References

A. EP 347066 A1 ("EP '066") (Exhibit 2)

The U.S. counterpart to EP 347066 A1 is U.S. Patent No. Re. 34,712, which is a reissue of U.S. Patent No. 4,593,590.

EP '066 teaches optically pure enantiomers of citalopram, and their use as anti-depressants.

In Example 3 of EP '066 (page 6, line 55, to page 7, line 7), the racemic citalopram diol precursor (II) was reacted with triethylamine and methanesulfonyl chloride. The reaction mixture was washed with 0.1M sodium hydroxide (NaOH), the organic phase was separated, and the solvent was evaporated. The resulting product was then dissolved in 2-propanol and methanol, and an equivalent amount of gaseous hydrobromide (HBr) was added. The mixture was left overnight to form the citalopram hydrobromide salt.

EP '066 does not disclose the purity of the citalopram base prepared in Example 3. Nor does EP '066 disclose a crystalline precipitate of citalopram free base.

Example 3 in EP '066 erroneously states that a crystalline base of citalopram was obtained by the experiment described therein. See page 7, lines 3-5, of EP '066. In fact, the experiment described in Example 3 results in the formation of the citalopram free base as an *oil*, not as a crystalline precipitate.

Submitted as Exhibit 5 is a May 3, 2002 declaration by Karl Anker Jørgensen, a professor in the Organic Chemistry department of Aarhus University, Denmark. Professor Jørgensen repeated the experiment described in Example 3 of EP '066 ten times. The product produced from each repetition of the experiment was an oil. No crystals were observed in the product, even after the product was allowed to sit for 6 days. Professor Jørgensen concludes:

> All the experiments have demonstrated that formation of Citalopram according to Example 3 of EP 347 066 gave the Citalopram base as an orange/brown oil and that crystals of the Citalopram base did not precipitate. The experiments also showed that no purification takes place during the process of said Example 3.

(Exhibit 5, point 6 on page 4).

Submitted as Exhibit 6 is a July 10, 2003 declaration by Professor Jørgensen stating that the Example 3 experiment was again carried out in the presence of six individuals who are not employees of the present assignee, H. Lundbeck A/S. As in the May 3, 2002 declaration, this experiment, too, was conducted in accordance with Example 3 of EP '066 and yielded an oil. No crystals formed even after the oil was allowed to sit for 24 hours and 12 days (see Exhibit 3, page 3, paragraph 11; and Exhibit 7, paragraphs 2 and 3). Professor Jørgensen concludes:

> The experiment has established that the formation of the citalopram base according to Example 3 of EP 0 347 066 A1 gives the citalopram base as an oil.

(Exhibit 6, point 14 on page 3).

Submitted as Exhibit 7 is a July 10, 2003 supplementary declaration by Professor Jørgensen further stating that the Example 3 experiment was conducted an additional seven times between April 8, 2003 and June 23, 2003 by two members of the Department of Chemistry at Aarhus University, Denmark, neither of whom are employed by the present assignee, H. Lundbeck A/S. Professor Jørgensen concludes:

> In all experiments, the Citalopram base was formed as a slightly yellowish oil or yellowish brown oil.

(Exhibit 7, point 4 on page 1).

EP '066 does not disclose a crystalline precipitate of citalopram free base as recited in pending claims 21-33.

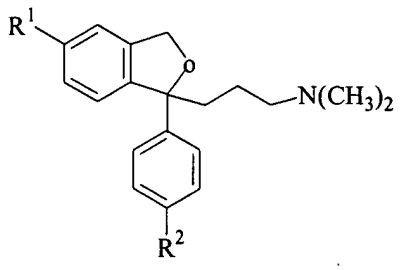
Therefore, applicants respectfully submit that Example 3 of EP '066 does not describe a reproducible crystalline precipitate of citalopram free base, and claims 21-33 are patentable over EP '066.

B. DE 2657013 (DE '013) (Exhibit 3)

The U.S. counterpart to DE '013 is U.S. Patent No. 4,136,193 ("the '193 Patent"). For convenience, all references below are to the '193 Patent (Exhibit 8) rather than DE '013.

Claims 21-33 are patentable over the '193 Patent, because the '193 Patent does not describe a crystalline base of citalopram, as recited in claims 21-33.

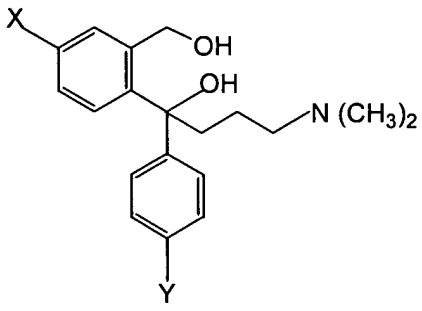
The '193 Patent describes compounds of formula (I) (shown below), including citalopram, which are useful for treating depression.



'193 Patent (I)

wherein R^1 and R^2 are halogen, trifluromethyl, cyano or RCO- wherein R is a C_{1-4} alkyl.

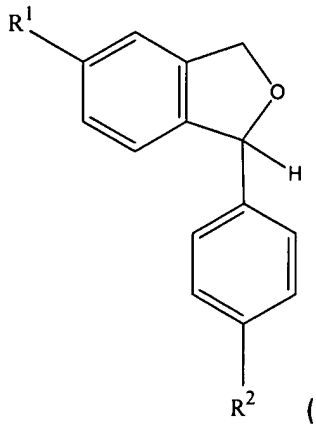
A method of forming the compounds of formula (I) is described at column 2, lines 9-33, by way of a precursor compound formula (II):



(II)

wherein X and Y are both halogen (for example bromo) or trifluoromethyl. This method is exemplified in Example 2, which discloses a method of making citalopram (see col. 6, lines 4-8).

At column 3, line 26, to column 4, line 3, the '193 Patent describes a second synthesis of the compounds of formula (I). In this synthesis, the compounds of formula (I) are prepared from a compound of formula (III)



(III)

wherein R^1 and R^2 are as defined above.

The '193 Patent does not describe forming the citalopram base in crystalline form, which is required by claims 21-33. In contrast, in the '193 Patent, the citalopram base was formed only as an oil. See col. 7, lines 20-25. As a result, claims 21-33 are patentable over the '193 Patent.

C. **WO 00/11926 (Exhibit 4)**

Claims 21-33 are patentable over WO 00/11926 (WO '926), because WO '926 does not describe or suggest precipitation of a crystalline base of citalopram.

WO '926 is directed to methods of making citalopram, by reacting a 5-bromo or 5-chloro citalopram precursor of formula (IV) with a cyanide source in the presence of a Ni catalyst. See page 3, lines 16-23. At page 4, lines 9-10, the specification states that "[b]y the process of the invention citalopram is obtained as a pure product in high yield thus reducing costly purification processes." In Example 1, at page 6, lines 19-32, citalopram was isolated in its salt form, as citalopram oxalate.

WO '926 nowhere describes or suggests the formation of citalopram in crystalline base form. In Example 1, in which citalopram oxalate is formed, the citalopram base is not crystallized. Rather, in Example 1 citalopram is formed in solution by reaction of 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-chlorophthalane with NaCN. The product is filtered and concentrated, the residue is dissolved in acetone and reacted with oxalic acid to form citalopram oxalate, which is isolated by filtration and recrystallized.

IV. Conclusion

In view of the foregoing, the PTO is requested to make this application special and to accelerate examination pursuant to 37 C.F.R. § 1.102(d) and M.P.E.P. §708.02(VIII).

Favorable action is earnestly solicited.

Respectfully submitted,

March 16, 2004

Jay P. Lessler
Registration No. 41,151
Attorney for Applicants

DARBY & DARBY, P.C.
Post Office Box 5257
New York, NY 10150-5257
Phone (212) 527-7700